Hepatocellular Carcinoma: Paradigm of Preventive Oncology

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ABSTRACT

Morbidity and mortality from hepatocellular carcinoma (HCC), which is primarily caused by hepatitis B virus or hepatitis C virus, can be prevented. *Public health interventions* have eliminated transfusion transmission of these viruses and, in endemic countries with effective hepatitis B virus vaccination programs, have greatly reduced incident hepatitis B virus infections (and HCC) in children. *Antiviral treatment* can eliminate detectable hepatitis C virus in 50%–80% of chronically infected patients, presumably reducing their risk of cancer. HCC survival rates remain universally poor, but *early detection and treatment* in developed countries has improved survival in selected patients. Despite these advances, worldwide HCC rates remain high, and additional preventive efforts are needed. The most important opportunity is wider distribution of hepatitis B virus vaccine in endemic areas. Development of an HCV vaccine, improved antiviral therapies, and better methods for HCC detection would also help decrease morbidity and mortality from HCC. HCC prevention efforts provide a paradigm for preventive oncology in cancers of viral etiology. *(Cancer J 2004;10:67–73)*

KEY WORDS

Epidemiology, hepatitis B virus, hepatitis C virus, hepatocellular carcinoma, liver, oncology, prevention, public health, treatment, vaccine

The growing list of cancers that are associated with viruses offers an important opportunity for preventive oncology. At least in theory, morbidity and mortality from cancers of viral etiology may be prevented in three ways. First, *public health interventions*, such as screening donated blood and vaccinating susceptible individuals, can decrease the incidence of infection with the oncogenic virus. Second, successful *antiviral treatment* may reduce cancer risk by eliminating (or markedly reducing) viral replication in infected patients. Finally, if infection with an oncogenic virus can be neither prevented nor treated, *early detection and treatment* of cancer may be effective in patients who are identified as being at high risk on the basis of their infection status. All of these approaches may be used to reduce the toll of hepatocellular carcinoma (HCC; Fig. 1), one of the most common causes of cancer mortality in the world.

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Received on February 4, 2004; accepted for publication March 3, 2004.

No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this article.

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HCC: INCIDENCE AND RISK FACTORS

In the year 2000, liver cancer, of which HCC is by far the predominant subtype, was the fifth most common cancer and the third most common cause of cancer death worldwide.[1] HCC displays striking international geographic variation (Fig. 2), with very high incidences in sub-Saharan Africa and Asia. Although HCC incidence is far lower in the United States and Europe,[2,3] those rates have been climbing in recent years.[4]

Most cases of HCC are due to infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), and studies of these associations provide some of the strongest evidence that viruses can cause cancer.[5] Worldwide, approximately 60% of HCC cases are attributable to HBV infection and approximately 25% to HCV.[6] Global patterns of infection with HBV and HCV account for most of the geographical heterogeneity in HCC rates. HBV infection is endemic in many parts of Asia and Africa,[1] where, in some cases, ingestion of aflatoxin acts synergistically with HBV to cause HCC. Recent increases in HCC rates in North America and Europe have been attributed largely to past increases in the prevalence of HCV infection,[7,8] but other factors, including an increased prevalence of obesity, may also contribute.[9] Although the prevalence of HCV is similar in Japan and the United States, HCC incidence is eight times higher in Japan. It is possible that this difference reflects genetic or environmental differences between these populations. However, because the latency period from infection with HCV to HCC development is 20–40 years,[10] the higher HCC rates in Japan may simply reflect the earlier spread of HCV in that country.[11] If so, the increased prevalence of HCV infection in the United States during the past

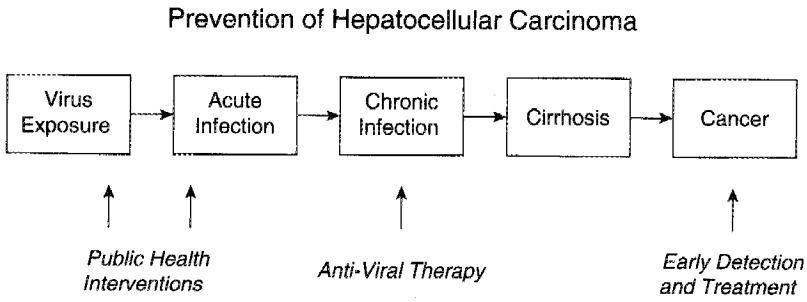

FIGURE 1 Prevention of hepatocellular carcinoma. Public health interventions (e.g., blood donor screening and vaccination) and antiviral treatments can reduce hepatocellular carcinoma (HCC) incidence. Early detection and treatment of HCC can reduce cancer mortality rates.

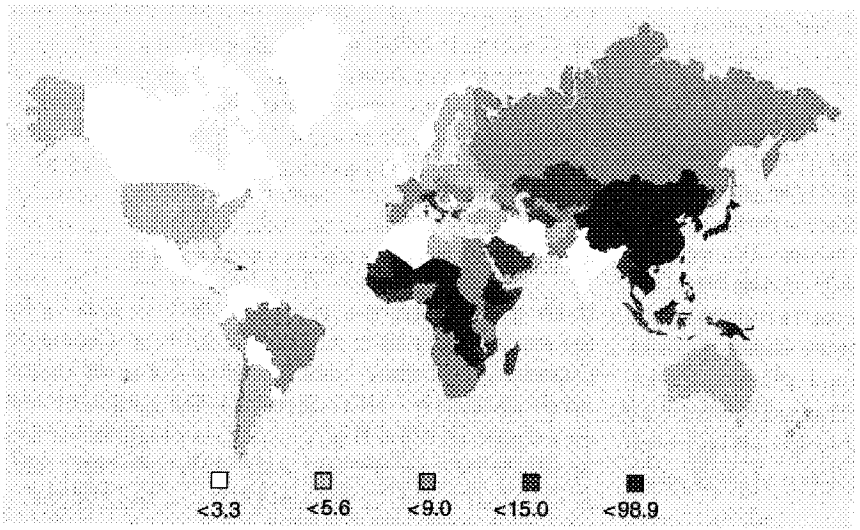

FIGURE 2 Worldwide incidence of primary liver cancer among men, age-standardized incidence per 100,000 population. (From Ferlay J, Bray F, Pisani P et al. GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide. Version 1.0. IARC CancerBase No. 5. Lyon, IARCPress, 2001. Used by permission.)

4 decades could lead to continued increases in HCC incidence in the United States.[12]

HBV

Although the clinical presentation and prognosis of HCC is similar, regardless of whether it results from HBV or HCV infection, the viruses themselves are quite different. HBV is a double-stranded DNA virus with reverse transcriptase properties, whereas HCV is an RNA virus. Infection with either virus can be either self-limited or chronic, but it is chronic infection that is strongly associated with increased risk of HCC.

The identification of HBV in the 1960s[13,14] led to serologic tests for this virus. Strong associations were made between regions with a high prevalence of HBV and a high incidence of HCC. In many parts of sub-Saharan Africa and East Asia, > 10% of the population is chronically infected with HBV. HBV may be transmitted perinatally, parenterally (through contaminated blood products or injection drug use), or sexually. In addition, HBV can be transmitted horizontally in early childhood, although the specific mechanism has not been well defined.[15] The risk of transmission is strongly related to the infectivity of the "donor." For example, HBV transmission is much likelier if HBV "e" antigen, a serologic marker of infectiousness, is present.[16]

Chronic infection with HBV is manifested by the continued expression of surface antigen (HBsAg) in the blood.[17] The reasons why HBV infection becomes chronic in some persons but not in others are incompletely understood, but age at infection is an important factor[18]—the younger the age of acute infection with HBV, the higher the risk of developing a chronic infection and becoming a "carrier." Children exposed to HBV perinatally have > 90% chance of chronic infection. With increasing age at the time of primary exposure, the risk of chronic HBV infection decreases from approximately 30% for children 5–10 years of age to < 5% for young adults.[18] Geographical areas that are endemic for HBV infection display a cycle in which carriers transmit HBV infect to young children. These young children are then themselves at high risk of becoming HBV carriers and, in turn, transmitting the virus to others.[16] In regions

where HBV transmission occurs primarily in adults, most infected persons resolve the infection and, therefore, fail to become HBV carriers.

Patients who are chronically infected with HBV are at high risk for subsequently developing chronic liver disease, cirrhosis, and HCC. The progression from infection to cancer occurs over several decades, and subjects may be asymptomatic until the disease is quite advanced.[19] About 20%–25% of all chronic carriers die of liver disease associated with HBV infection.[20] Chronic infection with HBV has been estimated to increase the risk of HCC by up to 100-fold.[21-23]

HCV

The discovery of HBV made it apparent that a so-called non-A, non-B hepatitis could be acquired through blood transfusion and cause chronic liver disease. Conventional virologic and immunologic approaches proved unsuccessful for discovering an non-A, non-B hepatitis virus. Using a complementary DNA (cDNA) library constructed from plasma of patients who were infected with the uncharacterized agent, Houghton and colleagues[24,25] identified a cDNA clone from the virus now known as HCV and demonstrated that HCV was the major cause of non-A, non-B hepatitis throughout the world. Phylogenetic analyses have classified HCV, a member of the Flaviviridae family, into six major genotypes (and at least 70 different subtypes)[26] that have implications for treatment responsiveness and, perhaps, clinical outcomes. Although not as common as HBV, infection with HCV is a global public health problem, with an estimated 170 million people infected worldwide.[7] HCV prevalence in the general population varies internationally. In the United States, 3.9 million people, or 1.8% of the population, are estimated to be infected with HCV.[27]

HCV is chiefly transmitted by exposure to infectious blood or blood-derived body fluids[28]; as a result, the distribution of HCV is very uneven. Sexual and perinatal HCV transmission can occur, but these routes are much less efficient. In the United States, injection drug use is the most common mode of HCV transmission, accounting for approximately 50% of new infections. HCV prevalence rates among injection drug users often exceed 90%. In less developed regions, the dominant routes of HCV transmission are less obvious, but transfusion of blood from HCV-infected donors, use of contaminated medical equipment, and ritualistic practices (e.g., scarification or tattooing) can lead to high rates of HCV infection.[29,30] In areas of rural Egypt where improperly sterilized syringes were used during a schistosomiasis eradication campaign, HCV prevalence now exceeds 20%.[31] A recent study in rural China found that the prevalence of HCV in 1990 was approximately 10% in a representative sample of the population older than 55 years,[32] possibly related to blood selling practices in the community.

Most people who are infected with HCV experience chronic infection with measurable viremia. The reported risk of chronic HCV infection varies from 86% (among asymptomatic blood donors who tested positive for HCV antibodies)[33] to 55% (among Irish women who had became infected through HCV-contaminated anti-D immune globulin 17 years earlier[34] and among young people who had undergone cardiac surgery during their first 3 years of life).[35] Prospective studies in Western populations indicate that about 20% of those first infected after age 40 experience cirrhosis after 20 years[36] and that the risk of cirrhosis is considerably lower among individuals who were infected at a younger age.[34,35,37] In the United States, the risk of HCC once cirrhosis is established is estimated to be 1%–4% per year.[8] In contrast, most Japanese patients with HCV-associated cirrhosis may die of HCC within 7 years.[38] Additional studies are needed to address these apparent differences.

PREVENTION OF HCC

Public Health Interventions

The knowledge that HCC is primarily caused by HBV and HCV is the basis for highly successful public health interventions against these viruses. Transmission of HBV and HCV through infected blood has been virtually eliminated in developed countries by measures such as abolishing payment for blood donations, screening potential donors for behavioral risks, and testing for viral antibodies and nucleic acids. As a result of these interventions, the risk of posttransfusion hepatitis in the United States decreased from 33% to nearly zero during the period from 1969 to 1998 (Fig. 3).[39] Persons with hemophilia also illustrate this success story. These patients were formerly at high risk for HBV and HCV infection, with infection rates exceeding 90%. This risk was eliminated by donor screening and the development of heat treatment of blood products.[40]

HBV vaccine programs illustrate the tremendous potential for reducing the incidence of virally associated cancers through vaccination. The HBV vaccine was the first vaccine designed to prevent a major human cancer, and it remains the only such vaccine in wide use. The initial vaccine was derived from plasma, but recombinant DNA technology has allowed production of HBsAg particles using yeast or mammalian cells. The recombinant vaccines are as efficacious as the plasma-derived version.[41]

Millions of people have been vaccinated against HBV

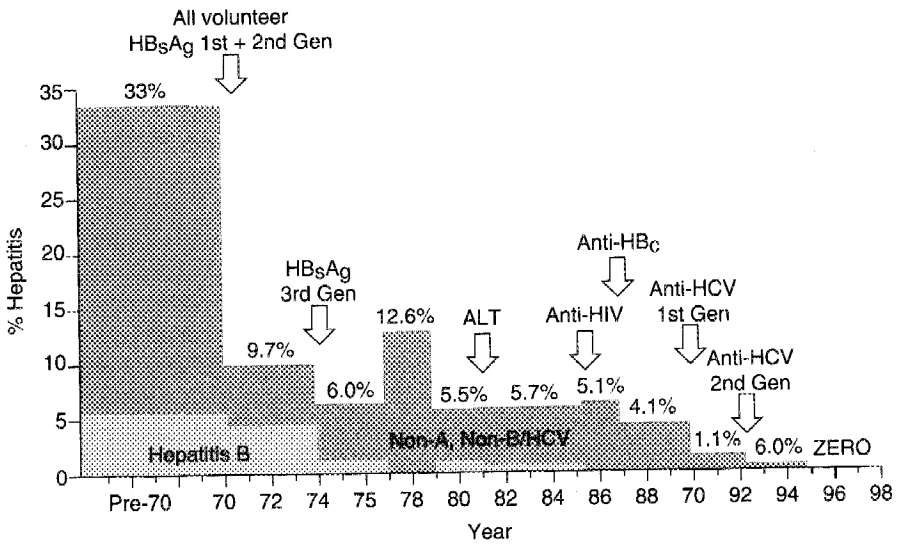

FIGURE 3 The decreasing incidence of transfusion-associated hepatitis in U.S. blood recipients, 1969–1998. Arrows indicate interventions in donor screening and selection (Adapted from Alter HJ, Houghton M. Hepatitis C virus and eliminating post-transfusion hepatitis. Nat Med 2000; 6:1082–1086.)

infection since the early 1980s, and adverse reactions to the vaccine are uncommon and generally mild. The HBV vaccine stimulates the production of antibodies to HBsAg. Field trials of the vaccine have demonstrated an 85%–95% efficacy in preventing chronic HBV infection,[42] and this response rate can reduce the prevalence of chronic HBV infection to less than 1% in children living in HBV-endemic regions. Nationwide data from Taiwan, which in 1984 was one of the first countries to introduce routine HBV vaccination, has documented a significant reduction in HCC rates among vaccinated children.[43] Because the highest risk for chronic HBV carriage is in newborns, the HBV vaccine is most effective when it is given as close to birth as possible. In many nonendemic countries in the developed world, HBV vaccination has also been introduced into the routine immunization program in accordance with World Health Organization recommendations. Targeted approaches focused on vaccinating individuals with behavioral (needle-sharing, multiple sexual partners, nonvaccinated adolescents) or occupational (health care workers) risk for HBV exposure continue in some regions.

Antiviral Therapy

HCC most often develops in patients with advanced cirrhosis. Treatments that lead to clearance of HBV or HCV should halt the progression of liver disease, thereby reducing the risk for HCC and other serious sequelae. Currently available treatments for chronic HBV infection have produced relatively low response rates.[44] Durable responses to HBV treatment resulting in viral eradication are infrequent, which suggests that prolonged therapy may be required to significantly modify outcomes such as HCC. Overall short-term response rates to either interferon-α or antiviral agents such as lamivudine, adefovir, or tenofovir remain in the 10%–35% range. Resistance to lamivudine, one of the most widely available and best tolerated anti-HBV agents, develops in almost all treated persons within a few years of therapy.

Recent advances in the treatment of HCV infection have greatly increased the likelihood of successful treatment of this infection. The combination of pegylated interferon-α and ribavirin results in nondetectable viral levels in about 50% of HCV-infected patients with genotype 1 (the most common genotype in North America) and in approximately 80% of patients with other genotypes.[45] Recent data suggest that treatment of chronic hepatitis may slow the progression toward cirrhosis and lessen the risk for HCC,[46] which has created optimism that HCC rates in the developed world may be reduced through effective therapy against HCV.

Early Detection and Treatment of HCC

Chronic infection with either HBV or HCV indicates an increased risk for HCC. Because most cases of HCC arise in a cirrhotic liver, liver biopsy can identify high-risk patients who may benefit from screening for HCC. Although there have been no randomized trials of such screening, observational data suggest that serial ultrasound examination and α-fetoprotein testing are useful for identifying early cases of HCC that may be more amenable to successful treatment.[47]

HCC is poorly responsive to systemic chemotherapy but is potentially curable by surgical resection, liver transplantation, or percutaneous treatment. The most appropriate course of therapy depends on the stage of the tumor and the degree of the underlying liver disease. Resection is often the treatment of choice for patients who have a single tumor and well-preserved liver function. Patients who have more advanced cirrhosis can be

treated with liver transplantation if they have no more than a few small tumors that have not metastasized.[47] Transplantation is markedly limited by a shortage of donor organs. In a recent review, Llovet and colleagues[47] suggested that these treatments can be applied to approximately 30% of patients who are diagnosed with HCC in the developed world and that resultant 5-year survival rates exceed 50%. These estimates should yield an overall 5-year survival rate of more than 15%. In the United States, however, the overall 5-year survival rate for HCC remains well below 10%, despite recent improvements.[48] Worldwide, most liver cancer occurs in persons who do not have access to screening and advanced treatments, and global 5-year survival for patients with HCC is reportedly less than 6%.[2]

FUTURE PROSPECTS

Prevention efforts for HCC have been highly successful compared with many other common tumors, but much more can be done to decrease morbidity and mortality from this neoplasm. Important areas of opportunity include wider distribution of HBV vaccine in endemic areas, development of an effective vaccine against HCV, improved antiviral therapies, and better methods for early detection of HCC.

Public Health Interventions

Vaccination to prevent HBV infection has been available for 2 decades, and when used in HBV endemic areas, it is one of the most cost-effective measures available to prevent early mortality in adults.[49] Despite its low cost (< $0.50 per pediatric dose), many countries with high rates of HBV-associated HCC cannot afford to purchase and deliver the vaccine. For example, few countries in sub-Saharan Africa have incorporated HBV vaccine into their routine immunization programs.

The Global Alliance for Vaccine and Immunizations (GAVI), in partnership with the World Health Organization and donor groups in the global health community, has focused on developing a vaccine-support strategy to remedy these disparities. With significant support from the Bill and Melinda Gates Foundation, GAVI is helping resource-limited countries provide HBV vaccine (and other childhood vaccines) to the world's children. In 2002, 10 million children residing in 33 countries that did not previously provide HBV vaccine were vaccinated as a result of this effort. By the end of 2004, it is anticipated that 160 of 200 (84%) countries worldwide will routinely provide the vaccine. Each additional 10 million children vaccinated is projected to prevent about 100,000 deaths due to HCC or other HBV-related conditions.[50]

The public health impact of HCV infection highlights the need for an effective HCV vaccine, but that effort has been impeded by challenging problems. First, although it appears that a vigorous polyclonal T-cell response plays a major role in the control of HCV infection, the specific immunologic factors associated with protection are not well defined.[51] Second, there is no reliable tissue culture system for propagating HCV. Third, chimpanzees are the only existing animal model for HCV infection. Finally, to be broadly effective, an HCV vaccine must generate protective immunity against various HCV genotypes. The sequence diversity of the HCV genome will make it challenging to create a globally effective vaccine. On the positive side, two candidate prophylactic vaccines have reached phase I clinical trials to study their safety in humans,[52] and the recent finding of cross-genotype immunity against HCV infection in chimpanzees provides hope for developing a vaccine protective against all HCV strains.[53]

Antiviral Therapy

Future cases of HBV infection can be prevented through vaccination, but that will not halt the development of HCC in the millions worldwide who are already infected with HBV. Better HBV treatment regimens are needed to reduce the risk of HCC in these people. Successful treatment of HBV will likely require combined antiviral and immune modulating approaches, which may minimize the development of resistant viruses.[46,54] These approaches may involve both better use of currently available drugs and discovery of novel agents. Numerous new therapeutic agents for treating HBV are under development; these include small molecules that inhibit polymerase activity, small interfering RNAs that reduce viral protein expression, and immunomodulatory approaches aimed at interleukins 12 and 18.[54]

Because current treatment regimens for HCV-infected patients are effective in only about 50% of those infected with HCV genotype 1, additional anti-HCV therapeutics are badly needed. Viral enzymes are essential for viral replication and therefore offer a potential drug target, as has been demonstrated for human immunodeficiency virus-1 infection. Investigators recently published a report demonstrating that a small-molecule HCV NS3 protease inhibitor was highly effective in reducing short-term HCV RNA plasma levels.[55] These preliminary results offer hope that the viral protease will prove to be a useful target for HCV therapeutics and that a higher proportion of patients will be effectively treated for HCV in the future.

Screening and Treatment

Better serologic screening tests might improve early detection of HCC in patients with advanced liver disease

due to HBV or HCV and may lead to better survival rates. The relatively poor specificity of conventional α-fetoprotein levels has led to a search for an HCC-specific α-fetoprotein. α-Fetoprotein has a single sugar chain, and structural heterogeneity of this chain has been utilized to aid in differentiating between benign and malignant liver disease. Based on their differential binding affinity for lectin, hepatoma-specific and nonhepatoma bands can be determined with improved sensitivity and specificity, although replication of these findings in larger populations is needed.[56,57] Other candidate tumor markers for HCC include des-gamma-carboxy prothrombin,[58] glypican-3,[59] and hepatoma-specific gamma-glutamyl transferase.[60]

Recent advances in mass spectrometry and bioinformatics may make discovery of novel HCC markers more feasible. The protein pattern (proteome) in a biologic sample can be examined by mass spectrometry.[61] Computer-assisted cluster analyses has been used to identify distinctive serum protein patterns that differentiate patients with ovarian, prostate, or breast cancers from healthy or precancerous counterparts[61-63] with fairly high sensitivity and specificity. Specific proteins that are abundant in patients with cancer can be identified by comparing these sequences with those in protein/peptide databases. These methods could potentially be used to identify patients with early HCC.

Circulating, cell-free DNA in serum or plasma may also provide an avenue for early detection of HCC. Mutations in the *p53* tumor suppressor gene are the most common genetic alteration in human cancer. Kirk and colleagues[64] demonstrated a very strong association of plasma 249 ser *p53* mutations with HCC in The Gambia but could also detect the mutation in a minority of individuals with cirrhosis and healthy controls. Other investigators have identified the same *p53* mutation in prediagnostic plasma specimens up to 5 years before diagnosis in half of HCC cases expressing the mutation in tissue.[65] Although 249 ser *p53* appears to be specific for HCC that is associated with aflatoxin, these findings demonstrate that serum DNA may identify individuals who are at high risk for developing HCC.

CONCLUSIONS

HCC prevention efforts provide a paradigm for reducing morbidity and mortality from cancers of viral etiology through *public health interventions* to prevent viral transmission, *antiviral treatment* of causative agents, and *early detection and treatment* of the cancer. Additional interventions are needed, and economic limitations currently prevent full implementation of our knowledge in populations that are most at risk for HCC. If these problems can be overcome, then the toll from HCC can be markedly decreased during the first half of this century.

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